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HbA_{1c} levels in non-diabetic Dutch children aged 8–9 years: the PIAMA birth cohort study

H. Jansen, A. H. Wijga*, H. A. Smit*, S. Scholtens†, M. Kerkhof, G. H. Koppelman‡, J. C. de Jongste§ and R. P. Stolk

Department of Epidemiology, University Medical Centre Groningen, University of Groningen, Groningen, *Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven, †Institute for Risk Assessment Sciences, Utrecht University, Utrecht, ‡Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, Groningen and §Department of Pediatrics, Division of Pediatric Respiratory Medicine, Erasmus University Medical Centre/Sophia Children's Hospital, Rotterdam, The Netherlands

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Abstract

Aim Glycated haemoglobin (HbA_{1c}) is considered the best index of glycaemic control in established diabetes. It may also be useful in the diagnosis of diabetes and as a screening tool. Little is known about the distribution of HbA_{1c} in healthy children and its predictors. The aim of this study is to describe the distribution of HbA_{1c} in non-diabetic Dutch children aged 8–9 years and to investigate potential associations of HbA_{1c} in this group.

Methods HbA_{1c} was measured in 788 non-diabetic children aged 8–9 years participating in the PIAMA birth cohort study. Data on parents and children were collected prospectively by questionnaires. Weight, height and waist and hip circumference of the children were measured when blood samples were taken.

Results Mean (SD) HbA_{1c} was $4.9 \pm 0.33\%$, range 3.5–6.0%. HbA_{1c} was significantly higher in boys (4.9 ± 0.31 vs. $4.9 \pm 0.33\%$) and in children of mothers with gestational diabetes (5.0 ± 0.37 vs. $4.9 \pm 0.32\%$). We found a significant inverse association between HbA_{1c} and haemoglobin (regression coefficient: –0.169 (95% CI –0.221 to –0.118), $P < 0.001$). HbA_{1c} was not significantly associated with age, body mass index, waist circumference, parental diabetes or maternal body mass index.

Conclusions We found no significant relation between known risk factors for Type 2 diabetes and HbA_{1c} at age 8–9 years. Moreover, there was a significant inverse association between haemoglobin and HbA_{1c}. These results suggest that HbA_{1c} may not only reflect the preceding blood glucose levels, but seems to be determined by other factors as well.

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Keywords children, glycated haemoglobin, non-diabetic

Abbreviations BMI, body mass index; HbA_{1c}, glycated haemoglobin; PIAMA, Prevention and Incidence of Asthma and Mite Allergy

Introduction

Glycated haemoglobin (HbA_{1c}) is currently considered the best index of glycaemic control for diabetic patients [1]. The level of HbA_{1c} is associated with the development and progression of microvascular complications [2] and with mortality in adults [3,4]. In addition, HbA_{1c} may be useful in the diagnosis of diabetes [5] and as a screening tool for detecting Type 2 diabetes in adults [6,7] and in children [8]. Compared with the oral glucose tolerance test, HbA_{1c} measurement is quicker and can be performed at any time of the day. Moreover, the consensus statement on the worldwide standardization of HbA_{1c} measurement of the Consensus Committee of the American Diabetes Association will contribute to worldwide comparability of HbA_{1c} results [9]. With the rapid increase in incidence and prevalence of diabetes, there will be an accompanying increased use of HbA_{1c} measurements in adults and in children. Therefore, it is important to develop reference levels and standards for HbA_{1c} for adults and children.

The normal distribution for HbA_{1c} for adults has been described and standardized by Simon *et al.* [10]. They found, in a population of 3240 healthy adults aged 40.2 ± 11.8 years,

Correspondence to: H. Jansen, Department of Epidemiology, University Medical Centre Groningen, University of Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: h.jansen@epi.umcg.nl

an approximately normal distribution of HbA_{1c}, with a slight difference between mean and median values at all ages in both sexes. There was no difference in mean HbA_{1c} according to gender: 5.0 ± 0.53% in men vs. 5.1 ± 0.55% in women. HbA_{1c} increased with deterioration of glucose tolerance and with all the known risk factors for diabetes (e.g. age, obesity and family history of diabetes). This study indicates that HbA_{1c} in adults is influenced only by factors closely linked to diabetes.

Although the normal distribution for HbA_{1c} has been described for adults, less is known about the distribution of HbA_{1c} in healthy children, particularly in those younger than 10 years. With the expected future increase in use of HbA_{1c}, it is important to develop reference levels and standards for HbA_{1c}. Moreover, HbA_{1c} could be an alternative measure to investigate early life and childhood determinants of impaired glucose tolerance and Type 2 diabetes in children. Therefore, the aim of this study is to describe the distribution of HbA_{1c} in a large population of Dutch children aged 8–9 years without diabetes mellitus and to investigate associations of HbA_{1c} in this group.

Methods

The study population consisted of 788 Dutch children born in the years 1996–1997 who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. Details of the study design have been published previously [11]. Recruitment took place in the years 1996–1997. A screening questionnaire on maternal allergy [12] was distributed to 10 232 pregnant women visiting one of 52 antenatal clinics in three different regions in the Netherlands (North, Central, West). Based on this screening, 7862 women were invited to participate in the study; 4146 agreed and gave written informed consent. Of those, 183 participants were lost to follow-up before any data on the child had been obtained, so that the study began with 3963 newborn children. Questionnaires were sent to the participating parents during pregnancy, at 3 months and yearly from 1 to 8 years of age. At 8 years of age, a subgroup of the study population (n = 1554), consisting of all children of allergic mothers (n = 988) and a random sample of the children of non-allergic mothers (n = 566), was invited for a hospital-based medical examination where a blood sample was taken and bronchial hyper-responsiveness was determined. From 1060 children, an EDTA blood sample was taken. Parents of 845 children gave informed consent to store plasma, erythrocytes and buffy coat for later analysis of parameters other than the asthma-related parameters. Parents of 826 children eventually gave written informed consent for the measurement of HbA_{1c} in the stored blood samples. Of these 826 samples, in 790 an HbA_{1c} value could be assessed. Two children with Type 1 diabetes were excluded from the current analyses.

For HbA_{1c} analysis, erythrocytes were stored at –20°C between 33 and 322 days prior to assay. A 5-µl cell mass was lysated and HbA_{1c} was measured by ion-exchange chromatography using the HA-8140 Hi-Auto HbA1c analyser (Menarini Diagnostics Benelux, Valkenswaard, The Netherlands). This analyser was standardized on Diabetes Control and Complications Trial (DCCT) standards. Between-batch imprecision (coefficient of variation) was 1.5% for a mean HbA_{1c} of 6.0% and 2.0% for a mean HbA_{1c} of 10.7%.

During the medical examination of the 8-year-olds, children were weighed and measured in their underwear. Weight was measured to 0.1 kg and height to 0.1 cm by trained research staff using calibrated measuring equipment. Body mass index (BMI) was calculated as weight/height squared (kg/m^2). 'Overweight' and 'obesity' were defined according to age- and gender-specific international standards [13]. We use the term 'overweight' for the group of children who are overweight but not obese. Waist circumference, to the nearest 0.1 cm, was measured midway between the lowest rib and the top of the iliac crest at the end of gentle expiration with a measuring tape. Hip circumference, to the nearest 0.1 cm, was measured at the greater trochanter. Waist and hip circumference were measured twice and the mean of the two measurements was used in the analysis. Birthweight data were obtained from the questionnaire sent to the participating parents 3 months after birth. Infant feeding data were collected by questionnaires at age 3 months and 1 year. These data were used to derive a variable categorized as never breastfed, less than 16 weeks breastfed and more than 16 weeks breastfed. Data on ethnicity of each parent (born in the Netherlands and of Dutch ethnicity, born in another Western country and of Dutch or another Western ethnicity, not born in a Western country or of non-Western ethnicity), educational level of each parent (three categories: low, intermediate and high), maternal BMI and parental diabetes were obtained by questionnaire. Parental educational level was defined as the highest educational level of father or mother. Data on lifestyle of the children, such as eating behaviour and hours spent watching television, were obtained from questionnaires sent to and filled out by the parents around the child's 8th birthday.

From the answers to the questions about eating behaviour, the variable 'snack score' was calculated. Parents answered questions about the frequency certain food and drink products were used, such as sweets and confectionery, fried snacks and soft drinks (there were five categories: never, less than once a week, on 1–2 days per week, on 3–5 days per week or on 6–7 days per week). All products were scored by a dietician on the basis of their average nutritional value (kcal) per portion, based on the average consumption of different types of the product, for example, diet and non-diet, in this age group. Thus, for each child, a snack score (kcal per week) was calculated.

Statistical methods

We used Student's t-test and one-way ANOVA to test for differences in mean HbA_{1c} between groups. Differences in HbA_{1c} between groups, adjusted for duration of sample storage, age and gender, were tested with ANCOVA. The relation between HbA_{1c} and continuous variables was tested with linear regression, with and without adjusting for duration of sample storage, age and gender. For all analyses, a level of significance of $P < 0.05$ was applied. All analyses were performed with SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

At 8 years of age, a subgroup of the study population, consisting of all children of allergic mothers and a random sample of the children of non-allergic mothers, was invited for a hospital-based medical examination. Therefore, offspring of allergic mothers were over-represented in our population. We repeated all analyses

Table 1 Characteristics of the study population

	Mean (SD)	*n* (%)
HbA$_{1c}$ (%)	4.9 ± 0.33	
Haemoglobin (mmol/l)	7.9 ± 0.44	
Sample storage (months)	5.9 ± 1.87	
Age (years)	8.1 ± 0.28	
Gender: girl (%)		387 (49.1)
Birthweight (kg)	3.52 ± 0.53	
Breastfeeding		
0 weeks		113 (15.2)
< 16 weeks		311 (42.0)
≥ 16 weeks		317 (42.8)
BMI (kg/m^2)	16.2 ± 1.89	
BMI		
Normal		683 (86.7)
Overweight		89 (11.3)
Obese		16 (2.0)
Waist–hip ratio	0.87 ± 0.04	
Region		
North		295 (37.4)
West		196 (24.9)
Central		297 (37.7)
Parental educational level		
Low		90 (11.4)
Intermediate		277 (35.2)
High		420 (53.4)
Maternal BMI (kg/m^2)	23.4 ± 3.63	
Parental diabetes:		21 (2.7)
Gestational diabetes:		24 (3.1)
Snack score (kcal/wk)	1699 ± 611	
Member of a sports club:		643 (87.5)
Time watching TV > 2 h:		55 (7.5)
Time playing outside > 3 times/week:		515 (69.9)

BMI, body mass index; HbA$_{1c}$, glycated haemoglobin; SD, standard deviation.

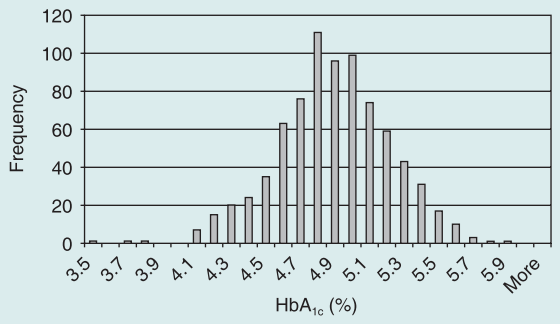

FIGURE 1 Distribution of glycated haemoglobin (HbA$_{1c}$). Mean (standard deviation) = 4.9 ± 0.33%.

in the two different groups: the offspring of allergic mothers and the offspring of non-allergic mothers.

Results

Characteristics of the study population are described in Table 1. Figure 1 displays the distribution of HbA$_{1c}$ in the whole study population. Mean (± SD) HbA$_{1c}$ was 4.9 ± 0.33% (range 3.5–6.0%). None of the children had an HbA$_{1c}$ > 6.0%. HbA$_{1c}$ was higher in boys compared with girls (Table 2). In addition, HbA$_{1c}$ was higher in children classified as obese compared with children classified as normal weight and overweight, although this was not statistically significant. HbA$_{1c}$ was significantly higher in children from the Northern region compared with children from the West and Central regions. Moreover, HbA$_{1c}$ was significantly higher in the offspring of mothers with gestational diabetes compared with the offspring of mothers without gestational diabetes.

HbA$_{1c}$ was higher in the offspring of obese mothers and in children watching television for more than 2 h per day, although these differences were not significant. HbA$_{1c}$ was not different between the children of parents with different educational levels. Of the 788 children, 733 (94.6%), 17 (2.2%) and 25 (3.2%) were of Dutch, Western and non-Western ethnicity, respectively. We found no differences in HbA$_{1c}$ between these groups (data not shown).

We found a significant relation between HbA$_{1c}$ and the duration of sample storage. HbA$_{1c}$ decreased by 0.001% (–0.001 to 0.000%) per day storage ($P < 0.001$). Mean HbA$_{1c}$ values, after adjusting for duration of sample storage, age and

Table 2 Clinical characteristics and HbA_{1c}

	HbA_{1c}			
	Crude mean	SD	Adjusted mean†	SD
Gender				
Girls	4.8	0.34	4.9	0.33
Boys	4.9	0.31	4.9*	0.31
Breastfeeding				
0 weeks	4.8	0.33	4.8	0.34
< 16 weeks	4.9	0.32	4.9	0.31
≥ 16 weeks	4.9	0.33	4.9	0.32
BMI				
Normal	4.9	0.32	4.9	0.31
Overweight	4.9	0.34	4.9	0.35
Obese	5.0	0.39	5.0	0.38
Region				
North	5.1*	0.31	5.0*	0.30
West	4.8	0.28	4.8	0.28
Central	4.8	0.31	4.8	0.31
Parental educational level				
Low	4.9	0.37	4.8	0.37
Intermediate	4.9	0.32	4.9	0.32
High	4.9	0.32	4.9	0.30
Maternal BMI				
Normal	4.9	0.32	4.9	0.31
Overweight	4.9	0.36	4.9	0.36
Obese	4.9	0.25	4.9	0.26
Parental diabetes				
Yes	4.9	0.26	4.8	0.30
No	4.9	0.33	4.9	0.32
Gestational diabetes				
Yes	5.1*	0.36	5.0*	0.37
No	4.9	0.32	4.9	0.32
Member of a sport club				
Yes	4.9	0.33	4.9*	0.32
No	4.8	0.32	4.1	0.31
Time watching TV				
≤ 2 h	4.9	0.33	4.9	0.32
> 2 h	5.0	0.27	4.9	0.28
Time playing outside				
≤ 3 times/week	4.9	0.32	4.9	0.32
> 3 times/week	4.9	0.33	4.9	0.32

*$P < 0.05$; †adjusted for duration sample storage, age and gender. BMI, body mass index; HbA_{1c}, glycated haemoglobin; SD, standard deviation.

gender, are given in Table 2. Most differences listed above remained. In addition, we found a lower mean (SD) HbA_{1c} in children who are not a member of a sports club (4.8 ± 0.31%) compared with children who are a member of a sports club (4.9 ± 0.32%). However, this finding could arise by chance.

We found a significant association between HbA_{1c} and haemoglobin, with a 0.169% (95% CI –0.221 to –0.118) decrease in HbA_{1c} (%) per mmol/l haemoglobin (adjusted for duration of sample storage, age and gender) ($P < 0.001$).

We found no significant association between HbA_{1c} and age in this population of children aged 8–9 years. There was also no significant association between the continuous variables of birthweight, anthropometric measures at 8 years (BMI, waist and hip circumference and waist–hip ratio), maternal BMI or snack score and HbA_{1c} ($P > 0.10$).

Because offspring of allergic mothers were over-represented in our population, we repeated all analyses in the offspring of allergic and non-allergic mothers separately. The results were similar in both groups.

Discussion

In this population of 788 non-diabetic Dutch children aged 8–9 years, HbA_{1c} is normally distributed, with a mean (SD) HbA_{1c} of 4.9 ± 0.33% (range 3.5–6.0%). HbA_{1c} is higher in boys compared with girls and in the offspring of mothers with gestational diabetes compared with the offspring of mothers without gestational diabetes. We also found a higher HbA_{1c} in children from the Northern region and an inverse association between haemoglobin levels and HbA_{1c}. We found no significant relation between HbA_{1c} and other known risk factors for Type 2 diabetes.

Saaddine *et al.* described the distribution of HbA_{1c} in children and young adults in the USA by use of data from the Third National Health And Examination Survey [14]. A total of 7974 non-diabetic children, adolescents and young adults aged 5–24 years were included. The overall mean (SD) HbA_{1c} was 5.0 ± 0.50%, varying from 4.9% (95% CI ± 0.04) in non-Hispanic whites, 5.1 ± 0.02% in Mexican-Americans and 5.2 ± 0.02% in non-Hispanic blacks. We included only children aged 8–9 years and in our study population, whereas 94.6% of the children were of Dutch ethnicity. The younger study population and differences in ethnicity could explain the difference in reported mean HbA_{1c}. As in our current study, Saaddine *et al.* also found a higher HbA_{1c} in men and in overweight participants. Pettitt *et al.* established the distribution of HbA_{1c} in 400 children aged 11–13 years [8]. They found a mean (SD) HbA_{1c} of 4.8 ± 0.39% (range 3.4–5.7%). In contrast to our data, they found no difference in HbA_{1c} between boys and girls.

Eldeirawi and Lipton investigated predictors of HbA_{1c} in almost 5000 non-diabetic children and adolescents aged 4–17.0 years. In their study population, HbA_{1c} also differed significantly between boys and girls, with boys having a higher HbA_{1c} than girls [15]. Also Shultis *et al.* found a higher HbA_{1c} in boys compared with girls [16].

In contrast to the studies of Eldeirawi and Lipton and Shultis *et al.*, we found no relation between HbA_{1c} and age. This could be explained by the very small age range in our study population.

We found a significantly higher HbA_{1c} in the children from the Northern region compared with the HbA_{1c} in children from West and Central regions. Controlling for potential confounding factors (duration of sample storage, age, gender, gestational diabetes of the mother and haemoglobin level) did not change this relation. There are no differences between the three regions in the way the blood samples were taken, processed and stored. Thus, the higher HbA_{1c} in children from the Northern region remains largely unexplained.

At least two studies have prospectively examined the role of exposure to diabetes *in utero* on childhood growth, later obesity and risk for Type 2 diabetes in the offspring [17,18]. In both studies, higher glucose concentrations and a higher prevalence of diabetes was found in the offspring of mothers with diabetes during pregnancy. This supports our finding of a higher HbA_{1c} in the offspring of mothers with gestational diabetes.

The negative association between haemoglobin and HbA_{1c} is in line with a decrease of HbA_{1c} after iron supplementation in iron-deficient patients [19,20]. Thus, HbA_{1c} levels are not only the result of preceding blood glucose levels and this should be taken into account when considering HbA_{1c} as a screening tool.

Birthweight is associated with greater insulin resistance in children [21,22]. However, in our study population, in the study population of Shultis *et al.* [16], as well as in Jamaican schoolchildren [23], no association was found between HbA_{1c} and birthweight. Breastfeeding recently has been suggested as being protective against the development of Type 2 diabetes in youth, mediated in part by current weight status in childhood [24]. In our study population, we found no association between HbA_{1c} and breastfeeding. Also in the study of Shultis *et al.*, breastfeeding initiation and exclusivity were not associated with HbA_{1c} in 1645 non-diabetic children aged 9–11 years [16]. Family history of diabetes is strongly associated with Type 2 diabetes in children [25,26]. However, as with Shultis *et al.* [16], we found no relation between parental history of diabetes and HbA_{1c} in children.

Taken together, we did not find an association between known risk factors for Type 2 diabetes and HbA_{1c} in children aged 8–9 years. At this young age, the increased insulin resistance as a result of these risk factors presumably is not yet present or is fully compensated for by increased insulin production, resulting in normal glucose and HbA_{1c} levels. Unfortunately, we did not assess insulin levels in our study.

Our study population is not representative of all Dutch children of similar age. It contains less overweight and obese children and ethnic minorities are under-represented. Several studies found higher HbA_{1c} levels in children from minority populations in the USA [9,14,16] and Shultis *et al.* found a slightly higher HbA_{1c} in children from non-white ethnic background in their study population of 1645 UK children (95.3% white, 4.7% non-white). In our study population, only 3.2% of the children were from non-Western origin, which is not representative of all Dutch children of similar age. Potential differences in HbA_{1c} between children from different ethnic groups in the Dutch population of children aged 8–9 years could be missed. In the PIAMA birth cohort study, pregnant women were recruited from the general population by means of a validated screening questionnaire on maternal allergy.

In this cohort of 788 non-diabetic Dutch children, HbA_{1c} was normally distributed. We found a higher HbA_{1c} in boys and in the offspring of mothers with gestational diabetes, compared with their counterparts. We found no significant relationship between HbA_{1c} and other known risk factors for Type 2 diabetes. Moreover, we found a significant inverse association between haemoglobin levels and HbA_{1c} and an unexplained higher HbA_{1c} in children from the north of the Netherlands. Thus, it could be argued that HbA_{1c} values should be interpreted with caution. They may not only reflect the preceding blood glucose levels, but seem to be determined by other factors as well.

Competing interests

Nothing to declare.

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